Autologous Ex Vivo Lentiviral Gene Therapy for Adenosine Deaminase Deficiency.

Journal: N Engl J Med

Publication Year: 2021

Authors: Donald B Kohn, Claire Booth, Kit L Shaw, Jinhua Xu-Bayford, Elizabeth Garabedian, Valentina Trevisan, Denise A Carbonaro-Sarracino, Kajal Soni, Dayna Terrazas, Katie Snell, Alan Ikeda, Diego Leon-Rico, Theodore B Moore, Karen F Buckland, Ami J Shah, Kimberly C Gilmour, Satiro De Oliveira, Christine Rivat, Gay M Crooks, Natalia Izotova, John Tse, Stuart Adams, Sally Shupien, Hilory Ricketts, Alejandra Davila, Chilenwa Uzowuru, Amalia Icreverzi, Provaboti Barman, Beatriz Campo Fernandez, Roger P Hollis, Maritess Coronel, Allen Yu, Krista M Chun, Christian E Casas, Ruixue Zhang, Serena Arduini, Frances Lynn, Mahesh Kudari, Andrea Spezzi, Marco Zahn, Rene Heimke, Ivan Labik, Roberta Parrott, Rebecca H Buckley, Lilith Reeves, Kenneth Cornetta, Robert Sokolic, Michael Hershfield, Manfred Schmidt, Fabio Candotti, Harry L Malech, Adrian J Thrasher, H Bobby Gaspar

PubMed link: 33974366

Funding Grants: Efficacy and safety of cryopreserved autologous CD34+ HSC transduced with EFS lentiviral vector encoding for human ADA gene in ADA-SCID subjects

Public Summary:
Abstract Background: Severe combined immunodeficiency due to adenosine deaminase (ADA) deficiency (ADA-SCID) is a rare and life-threatening primary immunodeficiency. Methods: We treated 50 patients with ADA-SCID (30 in the United States and 20 in the United Kingdom) with an investigational gene therapy composed of autologous CD34+ hematopoietic stem and progenitor cells (HSPCs) transduced ex vivo with a self-inactivating lentiviral vector encoding human ADA. Data from the two U.S. studies (in which fresh and cryopreserved formulations were used) at 24 months of follow-up were analyzed alongside data from the U.K. study (in which a fresh formulation was used) at 36 months of follow-up. Results: Overall survival was 100% in all studies up to 24 and 36 months. Event-free survival (in the absence of reinitiation of enzyme-replacement therapy or rescue allogeneic hematopoietic stem-cell transplantation) was 97% (U.S. studies) and 100% (U.K. study) at 12 months; 97% and 95%, respectively, at 24 months; and 95% (U.K. study) at 36 months. Engraftment of genetically modified HSPCs persisted in 29 of 30 patients in the U.S. studies and in 19 of 20 patients in the U.K. study. Patients had sustained metabolic detoxification and normalization of ADA activity levels. Immune reconstitution was robust, with 90% of the patients in the U.S. studies and 100% of those in the U.K. study discontinuing immunoglobulin-replacement therapy by 24 months and 36 months, respectively. No evidence of monoclonal expansion, leukoproliferative complications, or emergence of replication-competent lentivirus was noted, and no events of autoimmunity or graft-versus-host disease occurred. Most adverse events were of low grade. Conclusions: Treatment of ADA-SCID with ex vivo lentiviral HSPC gene therapy resulted in high overall and event-free survival with sustained ADA expression, metabolic correction, and functional immune reconstitution. (Funded by the National Institutes of Health and others; ClinicalTrials.gov numbers, NCT01852071, NCT02999984, and NCT01380990.).

Scientific Abstract:
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